

CLAIMS

What is claimed is:

1. A method of modulating expression of an endogenous cellular gene in a
5 cell, the method comprising the step of:
 contacting a first target site in the endogenous cellular gene with a designed or
 selected zinc finger protein, wherein the protein comprises a functional domain;
 thereby modulating expression of the endogenous cellular gene.
- 10 2. The method of claim 1, wherein the step of contacting further comprises
 contacting a second target site in the endogenous cellular gene with a second zinc finger
 protein.
- 15 3. The method of claim 2, wherein the first and second target sites are
 adjacent.
- 20 4. The method of claim 3, wherein the first and second zinc finger proteins
 are covalently linked.
- 25 5. The method of claim 1, wherein the first zinc finger protein is a fusion
 protein comprising at least two regulatory domains.
6. The method of claim 3, wherein the first and second zinc finger proteins
 are fusion proteins, each comprising a functional domain.
7. The method of claim 6, wherein the first and second zinc finger protein are
 fusion proteins, each comprising at least two functional domains.
- 30 8. The method of claim 1, wherein the cell is selected from the group
 consisting of animal cell, a plant cell, a bacterial cell, a protozoal cell, or a fungal cell.

9. The method of claim 8 wherein the cell is a plant cell.
10. The method of claim 8, wherein the cell is a mammalian cell
- 5 11. The method of claim 10, wherein the cell is a human cell
12. The method of claim 1 wherein the expression of the endogenous cellular gene is repressed.
- 10 13. The method of claim 12, wherein the functional domain is selected from the group consisting of unliganded thyroid hormone receptor (TR), v-erbA, Dax, RBP, MeCP2, MBD2B and a DNMT.
14. The method of claim 1, wherein the expression of the endogenous cellular
15 gene is activated.
15. The method of claim 14, wherein the functional domain is ligand-bound thyroid hormone receptor.
- 20 16. The method of claim 15, wherein the ligand is 3,5,3'-triiodo-L-thyronine (T3).
17. The method of claim 1 wherein the functional domain is a bifunctional domain (BFD).
- 25 18. The method of claim 17, wherein the activity of the bifunctional domain is dependent upon interaction of the BFD with a second molecule.
19. The method of claim 18, wherein the BFD is selected from the group
30 consisting of thyroid hormone receptor, retinoic acid receptor, estrogen receptor and glucocorticoid receptor.

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20. The method of claim 18, wherein the second molecule is a protein.
21. The method of claim 18, wherein the second molecule is a small molecule.
22. The method of claim 19, wherein the second molecule is a small molecule.
23. The method of claim 22, wherein the small molecule is selected from the group consisting of thyroid hormone (T3), all-*trans*- retinoic acid, estradiol, tamoxifen, 4-
10 hydroxy-tamoxifen, RU-486 and dexamethasone.
24. The method of claim 1, wherein the method further comprises the step of first administering to the cell a delivery vehicle comprising the zinc finger protein, wherein the delivery vehicle comprises a liposome or a membrane translocation
15 polypeptide.
25. The method of claim 1, wherein the zinc finger protein is encoded by a zinc finger protein nucleic acid operably linked to a promoter, and wherein the method further comprises the step of first administering the nucleic acid to the cell in a
20 lipid:nucleic acid complex or as naked nucleic acid.
26. The method of claim 1, wherein the zinc finger protein is encoded by an expression vector comprising a zinc finger protein nucleic acid operably linked to a promoter, and wherein the method further comprises the step of first administering the
25 expression vector to the cell.
27. The method of claim 26, wherein the expression vector is a viral expression vector.

28. The method of claim 27, wherein the expression vector is selected from the group consisting of a retroviral expression vector, an adenoviral expression vector, and an AAV expression vector.

5 **29.** The method of claim 25, wherein the zinc finger protein is encoded by a nucleic acid operably linked to an inducible promoter.

30. The method of claim 26, wherein the zinc finger protein is encoded by a nucleic acid operably linked to an inducible promoter.

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31. The method of claim 1, wherein the target site is upstream of a transcription initiation site of the endogenous cellular gene.

32. The method of claim 1, wherein the target site is adjacent to a transcription
15 initiation site of the endogenous cellular gene.

33. The method of claim 1, wherein the target site is downstream of a transcription initiation site of the endogenous cellular gene.

20 **34.** The method of claim 1, wherein the zinc finger protein comprises an SP-1 backbone.

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